IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	§	
	§	
Donald L. MORTON *et al.*	§	
	§	Group Art Unit: 1813
Serial No.: 07/431,533	§	
	§	Examiner: M. Davis
Filed: November 3, 1989	§	
	§	Atty. Dkt.: CADL:002/HYL
For: URINARY TUMOR ASSOCIATED ANTIGEN, ANTIGENIC SUBUNITS AND METHODS OF DETECTION	§	

DECLARATION UNDER 37 C.F.R. §1.132 OF JOHN E. SHIVELY

BOX AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

I, John E. Shively, declare that:

1. I am Chairman of the Division of Immunology at the Beckman Research Institute of the City of Hope. I have held this position for 11 years and have worked on tumor antigens

for 21 years. I also am an expert protein chemist and am familiar with methods of protein purification, characterization, and structural analysis. A copy of my *curriculum vitae* is attached.

2. I have reviewed the abstract of Euhus *et al.*, *24th Annual Meeting of the American Society of Clinical Oncology* proceedings, May 22-24, 1988, and the claims pending in the above-captioned patent application. It is my understanding that the examiner in charge of the above-captioned application has alleged that the Euhus abstract enables one skilled in the arts of protein purification to isolate UTAA (urinary tumor associated antigen) from the sera of melanoma patients.

3. As an expert in the field, I believe that the Euhus abstract does not contain sufficient information to enable purification of UTAA. Furthermore, based on a comparison of this abstract and subsequent articles (Euhus *et al.*, *Int. J. Cancer*, 45:1065-1070, 1990, and Euhus *et al.*, *Cancer Immunol. Immunother.*, 32:214-220, 1990), it is my opinion that the antigen as described in the abstract was not purified to homogeneity, nor characterized sufficiently to allow even an expert to positively identify the same antigen. This opinion is based on the stated fact in the abstract that UTAA was usually isolated as an antigen-antibody complex in a fraction containing other antibody complexes. Such an unfractionated complex must contain many other antibodies and proteins irrelevant to UTAA and its cognate antibodies. They also state that some sera were free of immune complexes, but insufficient information was given on how to identify such sera, or how to modify the isolation procedure to successfully isolate the antigen in these distinct circumstances. In subsequent articles (cited above), the authors describe further

purification steps and primary evidence (Coomassie Blue stained gels and Western blots) that convincingly establish a method or purification, the purity and the molecular mass of UTAA.

4. While the examiner is correct that molecular masses reported from SDS gels are often in error by 10%, it also is true that this potential error leads to a source of confusion in the identification of proteins from one lab to another. Thus, the specific details of a given protein purification are critical to the establishment of identity of a protein. In the case of UTAA, sufficient detail to reproduce the purification and identification of UTAA was not available until the later, more detailed publications. It is clear to me that the Euhus abstract was a preliminary report, presenting evidence that such an antigen may exist and may be isolated given sufficient work. Indeed, more convincing proof was established in later work.

5. I hereby declare that all statements made herein of my knowledge are true and that all statements made herein on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under § 1001 of Title 18 of the U.S. Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

9/9/98
DATE

John E Shively
JOHN E. SHIVELY

CURRICULUM VITAE

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Education:

University of Illinois, Urbana - B.S. -1968 - Chemistry
University of Illinois, Urbana - M.S. -1969 - Biochemistry
University of Illinois, Urbana - Ph.D.- 1975 - Biochemistry

Positions:

9/75 - 11/76	Junior Research Scientist, Department of Immunology, City of Hope National Medical Center, Duarte, CA.
11/76 - 7/77	Assistant Research Scientist, Division of Immunology, City of Hope National Medical Center, Duarte, CA.
7/77 - 10/84	Associate Research Scientist, Division of Immunology, City of Hope National Medical Center, Duarte, CA.
7/77 - 12/86	Director of Immunochemistry, Division of Immunology, City of Hope National Medical Center, Duarte, CA.
10/84 -Present	Research Scientist, Division of Immunology, Beckman Research Institute of the City of Hope, Duarte, CA.
1/87 - Present	Chairman, Division of Immunology, Beckman Research Institute of the City of Hope, Duarte, CA.

Societies:

American Society of Biological Chemists and Molecular Biologist
American Association for the Advancement of Science
American Association for Cancer Research
Protein Society

Publicatons: John E. Shively, Ph.D.

1. Lewis, M. R. and Shively, J. E. Maleimidocysteinyl-DOTA derivatives: new reagents for radiometal chelate conjugation to antibody hinge sulfhydryl groups undergo pH-dependent cleavage reactions. Bioconjugate Chemistry. Vol. 9, 72-86, 1998.

2. Williams, L. E., Lewis, M. R., Bebb, G., Clarke, K. G., Odom-Maryon, T. L., Shively, J. E., and Raubitscheck, A. A. Biodistribution of ^{111}In-labeled and 90Y DOTA and maleimidocysteineamido-DOTA conjugated to chimeric anti-CEA monoclonal antibody in xenograft-bearing nude mice: comparison of stable and chemical labile linker systems. Bioconj. Chem. Vol. 9, 87-93, 1998.

3. Chen, D. S., Ananaka, M., Chen, F. S., Shively, J. E., and Lai, M. M. Human carcinoembryonic antigen and biliary glycoprotein can serve as mouse hepatitis virus receptors. J. Virol. Vol. 71, 1688-1691, 1997.

4. Hefta, J. J. F., Neumaier, M., and Shively, J. E. Kinetic and affinity constants of epitope specific anti-carcinoembryonic antigen (CEA) monoclonal antibodies for CEA and engineered CEA domain constructs. Immuno Technology. In Press, 1997.

5. Neumaier, M., Gaida, F.-J., Lewis, M. R., Hefta, L. J., Shively, L. E., Raubitscheck, A., and Shively, J. E. A chimeric anti-CEA antibody with heavy interchain disulfide bonds deleted: Molecular characterization and biodistributions in normal and tumor bearing mice. Submitted, 1997.

6. Neumaier, M., Shively, L. E., Raubitschek, A. A., and Shively, J. E. Expression and biodistributions in xenograft bearing nude mice of a monovalent, heavy chain disulfide bond deleted chimeric anti-carcinoembryonic antigen antibody. Antibody Technology. Submitted, 1997.

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11. Hu, S., Shively, L., Raubitscheck, A. A., Sherman, M., Williams, L. E., Wong, J. Y. C., Shively, J. E., and Wu, A. M. Minibody: A novel engineered anti-CEA antibody fragment (single-chain Fv-C_H3) which exhibits rapid, high-level targeting of zenografts. Cancer Res. Vol. 56, 3055-3061, 1996.

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glycoprotein: Demonstration of identity with BGP1. J. Biol. Chem. Vol. 268, 13015-13018, 1993.
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